DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed 2-28-08.

Claim 62 have been amended. Claims 70-83 have been cancelled.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. The rejection of claims 62-63 and 66-69 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for the reasons set forth in the previous office action.

The following Applicant arguments and Examiner arguments address the written description and enablement rejections separately.

Applicant arguments:

The Examiner alleges on pages 3-4 of the Office Action that Applicant was not in possession of the invention. Applicant respectfully disagrees and points at least to the passages on page 44, line 24, through page 46, line 12 for written description support of the claims as amended. For example, lines 1-7 of page 46 provide a detailed description of Applicant's invention as presently claimed:

Although applicants are not bound by the mechanism, it is believed that the ability of the immunostimulatory nucleic :acids to prevent the development of resistant strains results from the ability of the nucleic acids to induce an immune response leading to an

improved response by the immune system against a microorganism. At the same time, the anti-microbial agent is functioning to kill or inhibit the microorganism. This dual action may result in rapid inhibition of the invading microorganism, reducing the time in which genetic modifications can occur prior to cell death or inhibition. This aspect of the invention is also explained at least on lines 6-14 of page 7, where the specification describes the advantage of combining agents that use different mechanisms for attacking microbial infections: The immunostimulatory nucleic acids when combined with the anti-microbial agents have many advantages over the use of each composition alone for the treatment of infectious disease. The immunostimulatory nucleic acids function in some aspects by simultaneously inducing innate and antigen specific immune responses leading to a multifaceted attack by the immune system on the microorganism. The anti-microbial agents specifically attack the microorganism, causing death or inhibition of the microorganism. The immunostimulatory nucleic acids provide long-lasting effects, thus reducing dosing regimes, improving compliance and maintenance therapy, reducing emergency situations; and improving quality of life. Applicant also provides a detailed description of different types of immunostimulatory nucleic acids and specific examples of immunostimulatory nucleic acids (see, for example, line 26 on page 7 through line 27 on page 18) that can be used to treat a microbial infection via an immunostimulatory mechanism in contrast to an antibiotic that directly attacks the microorganism responsible for the microbial infection. In addition, Applicant provides a detailed description of different types of antibiotics and specific examples of antibiotics (see, for example, line 16 on page 26 through Table 2on page 34) that can be usedto treat a microbial infection.

The Examiner pointed to publications by Krieg et al. and Mutwiri et al. to support the proposition that Applicant was not in possession of the invention. Applicant respectfully disagrees with the Examiner's position and submits that these publications fail to negate Applicant's detailed explanation of the invention and detailed description of the structures and functions of the immunostimulatory nucleic acids and antibiotic agents that can be used together to prevent the development of antibiotic resistant microbial infections. The observation that certain immunostimulatory oligonucleotides have

different levels of activity does not undermine the claimed invention in the same way that different levels of activity observed for different antibiotics do not undermine the claimed invention. Indeed, Applicant refers throughout the specification to different factors that should be considered when selecting immunostimulatory nucleic acids and antibiotics.

Applicant arguments:

The Examiner alleges on pages 5-10 of the Office Action that the invention was not enabled. Applicant respectfully disagrees and submits that the amended claims recite features that are described in such a way that one or ordinary skill in the art would be able to practice the invention without undue experimentation.

The claims as amended recite administering to a subject prior to, at the same time as or after the subject has received antibiotic therapy against a microbial infection an effective amount of an immunostimulatory nucleic acid for promoting an immune response against the microbial infection, thereby preventing the development of an antibiotic resistant microbial infection. Applicant respectfully submits that one of ordinary skill in the art can identify or administer an antibiotic against a microbial infection as described in the specification. Applicant further submits that one of ordinary skill in the art can administer an immunostimulatory nucleic acid as claimed based on the teachings of the specification. As described above, the specification provides a detailed description of antibiotics, immunostimulatory nucleic acids, and methods for administering them to prevent the development of antibiotic resistant microbial infections.

On pages 5-10 of the Office Action, the Examiner provided a number of collateral lines of evidence based on the alleged state of the art to support the position that "the state of the art is unpredictable with regard to preventing antibiotic resistance" and thus the instant claims are not enabled. Applicant respectfully submits that the Examiner's interpretation as presented in the Office action is inconsistent with case law, in view of which Applicant presents arguments below.The Examiner cited Krieg et al. for the

proposition that "each immunostimulatory nucleic acid must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies." The Examiner cited Mutwiri et al. for the proposition that "the immunostimulatory activity of oligonucleotides containing the CpG is very species specific." The Examiner stated that "Yamamoto et al. reports that oligonucleotides containing the CpG motif failed to improve the survival in mice challenged with influenza." The Examiner also cited Gura for the proposition that "synthetic oligonucleotides have caused side effects in experimental animals." Applicant does not agree with the conclusions drawn by the Examiner. However, taken on their face, the cited references point out certain variations in responses to immunostimulatory CpG oligonucleotides. However, Applicant submits that these variations do not negate the claimed invention. Applicant respectfully disagrees with the implied notion that such variations amount to unpredictability or undue experimentation. Variations associated with therapeutics amongst species, or in some cases amongst individuals of the same species, are to be expected. Like any therapeutic reagent, therefore, it is reasonably expected that optimal effects of the immunostimulatory oligonucleotides of the instant invention can depend on various factors, as noted by the Examiner, such as various modes of administration. Applicant does not dispute the notion. In fact, even with an FDA-approved drug, a certain degree of optimization is required. That in itself, however, does not render the claimed invention unpatentable. Chapter 2100 of the MPEP states, "An applicant's specification must enable a person skilled in the art to make and use the claimed invention without undue experimentation. The fact that experimentation is complex, however, will not make it undue if a person of skill in the art typically engages in such complex experimentation." Given the amount of information provided regarding CpG nucleic acids and the antibiotic agents, the skilled artisan would have no trouble implementing the invention as claimed. That is, the skilled artisan would know how to make and prepare a composition comprising an immunostimulatory nucleic acid as described in the specification and administering it to a subject in addition to an antibiotic. In addition, the skilled artisan would know how to optimize the same, based on the various parameters as presented in the detailed description.

In conclusion, a number of references were cited in the office action. However, it is unclear to Applicant as to how each of the cited references supports the Examiner's positioh that the instantly claimed invention lacks enablement. In particular, Applicant notes that the cited references do not necessarily contradict the essence of the present invention.

The Examiner also stated that "the specification does not contain any working examples that are directed to the claimed invention" and argued that the specification "does not provide any evidence that the claimed method would function in vivo or in vitro." Finally, the Examiner concluded that "it would require undue experimentation for one skilled in the art to use the claimed methods."

Examiner's Response to Applicant's Arguments:

The Examiner accepts that the passages on page 44, line 24, through page 46, line 12 for written description support of the claims as amended and lines 1-7 of page 46 provide a description of invention as presently claimed. However, a description of different types of antibiotics and specific examples of antibiotics (see, for example, line 16 on page 26 through Table 2on page 34) that can be used to treat a microbial infection. However the method is drawn to a method for preventing the development of an antibiotic resistance microbial infection, the method comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy against the microbial infection, an effective amount of an immunostimulatory nucleic acid for promoting an immune response against the microbial infection, thereby preventing the development of an antibiotic resistant microbial infection. The disclosure fails to set forth the complete structure of an oligonucleotide that prevents antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. The disclosure further failed to set forth the physical and chemical properties of oligonucleotides encompassed by the claimed invention. Furthermore, the disclosure failed to set forth any functional characteristics that the immunostimulatory nucleic acids must possess to prevent antibiotic resistance.

The reference by Krieg, teaches that each immunostimulatory nucleic acid must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies (see Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. (paragraph that bridge pages 716-717, in particular)). Additionally Mutwiri et al teaches that the immunostimulatory activity of oligonucleotides containing the CpG is very species specific. Therefore since the specification does not disclose any functional characteristics that the immunostimulatory nucleic acids must possess to prevent antibiotic resistance the written description has been maintained.

Examiner's Response to Applicant's Arguments:

Examiner accepts the amendments to the claim. However Applicant's arguments are not persuasive. However the claims are still broadly drawn to any immunostimulatory nucleic acid to promote an immune response against the microbial infection in a subject. The methods for confirming the effectiveness of an immunostimulataory nucleic acid, by promoting an immune response against the microbial infection are not disclosed discussed throughout the specification. Furthermore prior art, discloses the unpredicatability and limitations of the claimed invention. Therefore based on the prior art, considerations of functional characteristics that the immunostimulatory nucleic acids must possess to prevent antibiotic resistance have not been met. Although the specification provides a description of the genus of immunostimulatory nucleic acids, as well as data demonstrating their immunostimulatory activity etc and antibiotics. The description and the data found in the specification does not establish a pattern of immune stimulation which is consistent with promoting an immune response against microbial infection. The data is not sufficient to establish to one of skill in the art that CpG oligonucleotides are sufficient to promote an immune response against the microbial infection, thereby preventing the development of an antibiotic resistant microbial infection. Therefore examiner disagrees that any immunostimulatory nucleic acid administered in the method can promote an immune

response against the microbial infection, thereby preventing the development of an antibiotic resistant microbial infection.

As outlined previously the claimed invention is directed toward a method to a method for preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. The basic inquiry for possession is: Can one skilled in the art reasonably conclude that the inventor was in possession of the claimed invention at the time the application was filed? If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claim is not explicitly described in the specification, then the requirement for an adequate written description is met.

To provide adequate written description and evidence of possession, the specification must provide sufficient description of the Claimed invention by i) actual reduction to practice or ii) disclosure of relevant identifying characteristics, such as disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, correlation between structure and function, and methods of making the claimed invention. The analysis: i) Sufficient description of the claimed invention by actual reduction to practice: The specification gives general references of antibiotic resistance, wherein the specification lists many examples of different infection. (i.e. bacterial infection). Also the specification list several antibiotics and immunostimulatory acid molecules that could be use in the claimed method (see pgs. 12-14, 25-30, and 45-50). The specification does not teach any method of using of an oligonucleotide comprising an immunostimulatory nucleic acid to prevent antibiotic resistance. In the instant, the disclosure fails to evidence that Applicant is in possession of the claimed invention by actual reduction to practice. ii) Disclosure of relevant identifying characteristics: The disclosure fails to provide relevant identifying characteristics relating to the claimed invention. The disclosure fails to set forth the complete structure of an oligonucleotide that prevents antibiotic resistance, comprising: administering to a

subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. The disclosure further failed to set forth the physical and chemical properties of oligonucleotides encompassed by the claimed invention. Furthermore, the disclosure failed to set forth any functional characteristics that the immunostimulatory nucleic acids must possess to prevent antibiotic resistance. As evidenced by Krieg, that teaches that each immunostimulatory nucleic acid must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies (see Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. (paragraph that bridge pages 716-717, in particular)). Additionally Mutwiri et al teaches that the immunostimulatory activity of oligonucleotides containing the CpG is very species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the in vitro immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif (see Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90). In the instant, the specification does not demonstrate that Applicant is in possession of an immunostimulatory nucleic acid to prevent antibiotic resistance therefore the skilled artisan cannot reasonably conclude or recognize that Applicant is in possession of the claimed invention at the time the invention was filed. Applicant is reminded that that written description requirement is separate and distinct from the enablement requirement.

As outlined previously claimed invention is directed toward a method to a method for preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance.

Nature of the invention. The claims are drawn to a method for preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. The specification does not teach any method nor does the specification teach any of the myriad of possibilities of any immunostimulatory nucleic acid molecule having the claimed formula can be used to prevent antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance.

The breadth of the claims. The product being used to administer to a subject (human or otherwise) stated in claim 62, an immunostimulatory nucleic acid is overly broad. The claims are drawn to a method for preventing any type of antibiotic resistance comprising administering to a subject (human or otherwise) prior, at the same time as or after the subject has received antibiotic therapy an effective amount of any immunostimulatory nucleic acid for preventing any type of antibiotic resistance. Therefore it is hard for one skilled in the art to determine if any immunostimulatory nucleic acid can be used for preventing any type of antibiotic resistance in a subject (human or otherwise). The quantity of experimentation required to practice the invention as claimed would require the determination of accessible target sites, modes of delivery and formulations, the route and time course of administration that encompass any immunostimulatory nucleic acid with limitations as discussed above to target appropriate cells and/or tissues in any and/or all organisms/subjects, and further whereby effects are provided for the claimed conditions. Since the specification fails to provide particular guidance for preventing any type of antibiotic resistance in a subject comprising administering to a subject prior to, at the same time as, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance and since determination of these factors for a particular immunostimulatory nucleic acid for

the particularly claimed conditions are not disclosed, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

The state of the prior art. The state of the art is unpredictable with regard to preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. The art teaches that each immunostimulatory nucleic acid must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies (see Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. (paragraph that bridge pages 716-717, in particular)). The art further teaches that the immunostimulatory activity of oligonucleotides containing the CpG is very species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the in vitro immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif. Mutwiri et al. also sets forth that in vitro observations do not accurately predict what happens in vivo (see Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90). Additionally, both Krieg et al. and Mutwiri et al. note that the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif; ii) the spacing between CpG motifs; iii) the numbers of CpG motifs in an oligonucleotide; iv) the absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG motif is presented in the sequence. Moreover, the potential use of oligonucleotides containing immunostimulatory nucleic acids that prevents infection is widely speculated in the art. However, efforts to harness the immunostimulatory activity of oligonucleotides to trigger an innate immune response that protect a host from infectious pathogen has proven to

be challenging and elusive, as evidenced by Yamamoto et al. Yamamoto et al. reports that oligonucleotides containing the CpG motif failed to improve the survival in mice challenged with influenza (see Yamamoto et al., Oligodeoxyribonucleotides with 5'ACGT-3' or 5TCGA-3 sequence induce production of interferons. Curr. Top. Microbiol. Immunol. 2000, Vol. 247, 23-40). Furthermore, major considerations for any nucleic acid therapy protocol involve issues such as the amount of oligonucleotide administered, what amount is considered therapeutically effective, the route and time course of administration, sites of administration. For example, Gura (Science vol. 270 p. 575-577, 1995, see p. 576 right column) teach that synthetic oligonucleotides have caused side effects in experimental animals and that when administered by one-time injection in high does, several phosphorothioates drugs were lethal to some of the animals. Furthermore, the oligonucleotides caused a transient decrease in two kinds of white blood cells as well as changes in blood pressure and heart rate. Such cardiovascular and other effects seen in animals can be minimized in patients using low does of the compounds and administering then gradually by continuous intravenous injection. Phosphorothioates have been found to accumulate in the liver, kidneys, and bone marrow of animals, although the long-term effects of this deposition are not clear (Gura). The art teaches that "immunomodulatory regimens offer an attractive approach as an adjunct modality for control of microbial diseases in the era of antibiotic resistance". The art teaches that there is a struggle to control infectious diseases and the immunostimulatory and immunosuppressive agents are capable of enhancing host defense mechanisms to provide protection against infections. The art teaches that when administering CpG ODN have given protection and partial protection against infections (see Masihi, K Expert Opin. Biol. Ther. July 2001, Vol. 1, No. 4, Pages 641-653 especially pg. 641-642, 646 and 648). The art teaches that "the spread of bacteria resistant to antimicrobial agents calls for population-wide treatment strategies to delay or reverse the trend toward antibiotic resistance, and that the treatment of all patients with a combination of antibiotics is in most cases the optimal strategy" (see BonHoefer et al 1997 Proc. Natl. Acad. Sci. Vol. 94 pgs. 12106-12111 in its entirety). Lastly there is no information on administering to a subject prior to, at the same time, or after the

subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. For the reasons set forth supra, the state of the art is unpredictable whether all immunostimulatory nucleic acids can prevent any type of antibiotic resistance in a subject.

Guidance in the specification/Working Examples. The specification does not contain any working examples that are directed to the claimed invention, a method for preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. The specification does not contain any working examples demonstrating that such immunostimulatory nucleic acids prevent any type of antibiotic resistance. The specification has not shown that the immunostimulatory nucleic acids contemplated by the claims prevent antibiotic resistance. The specification gives general references of antibiotic resistance, wherein the specification lists many examples of different infection. (i.e. bacterial infection). Also the specification list several antibiotics and immunostimulatory acid molecules that could be use in the claimed method (see pgs. 12-14, 25-30, and 45-50). The specification only speculates administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance oligonucleotides in a subject. It is noted that the specification describes the steps of the claimed method to one skilled in the art, but does not provide any evidence that the claimed method would function in vivo or in vitro. The issue of correlation is related to the issue of the presence or absence of working examples. Correlation as used herein refers to the relationship between in vitro or in vivo animal model assays and disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a working example, if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples. (see MPEP 2164.02) The pending specification does not set forth such correlations for a working example of the claimed in vivo method. As stated above, the

specification has not provided much, if any, guidance or direction nor given any working examples relating to the claimed invention. In the instant, while the guidance or direction of research may be outlined for the skilled artisan, the skilled artisan would not readily be able to practice the claimed invention without the undue burden of experimentation. Therefore, the specification fails to enable the claimed invention.

In conclusion, the claimed inventions are not enabled for preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of any immunostimulatory nucleic acid for preventing antibiotic resistance. The product being used to administer to a subject stated in claim 62 is overly broad for preventing any type of antibiotic resistance. There is insufficient direction or guidance is presented in the specification using the claimed method for preventing antibiotic resistance. There are no working examples presented in the specification that teach the claimed method for preventing antibiotic resistance. The state of the art shows immunostimulatory nucleic acids must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. Lastly there is no information on administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance which renders the method for preventing antibiotic resistance unpredictable. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nina A Archie/
Examiner, Art Unit 1645
/N. A. A./
Examiner, Art Unit 1645

Nina A Archie
Examiner
GAU 1645
REM 3B31
/Mark Navarro/

Primary Examiner, Art Unit 1645